View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

Volume 12 • Number 2 • 2009
VALUE IN HEALTH

Information on Center Characteristics as Costs' Determinants in Multicenter Clinical Trials: Is Modeling Center Effect Worth the Effort?

Michele Petrinco, PhD Student,[1] Eva Pagano, BCs,[2] Alessandro Desideri, PhD,[3] Riccardo Bigi, MD, PhD, FE SC,[4] Marco Ghidina, BSc,[5] Alberto Ferrando, BSC,[2] Lauro Cortigiani, MD,[6] Franco Merletti, MD,[2] Dario Gregori, MA, PhD[7]

[1]Department of Public Health and Microbiology and Department of Statistics and Applied Maths "Diego de Castro," University of Turin, Turin, Italy; [2]Unit of Cancer Epidemiology, University of Turin, CERMS and CPO-Piemonte, Turin, Italy; [3]Cardiovascular Research Foundation, San Giacomo Hospital, Veneto, Italy; [4]Cardiology Institute, University School of Medicine and Centro Diagnostico Italiano Milan, Italy; [5]Department of Cardiopulmonary Sciences, Ospedale S. Maria Della Misericordia, Udine, Italy; [6]Cardiovascular Unit, "Campo di Marte" Hospital, Lucca, Italy; [7]Department of Public Health and Microbiology, University of Turin, Turin, Italy

ABSTRACT

Objectives: Several methodological problems arise when health outcomes and resource utilization are collected at different sites. To avoid misleading conclusions in multi-center economic evaluations the center effect needs to be taken into adequate consideration. The aim of this article is to compare several models, which make use of a different amount of information about the enrolling center.

Methods: To model the association of total medical costs with the levels of two sets of covariates, one at patient and one at center level, we considered four statistical models, based on the Gamma model in the class of the Generalized Linear Models with a log link, which use different amount of information on the enrolling centers. Models were applied to Cost of Strategies after Myocardial Infarction data, an international randomized trial on costs of uncomplicated acute myocardial infarction (AMI).

Results: The simple center effect adjustment based on a single random effect results in a more conservative estimation of the parameters as compared with approaches which make use of deeper information on the centers characteristics.

Conclusions: This study shows, with reference to a real multicenter trial, that center information cannot be neglected and should be collected and inserted in the analysis, better in combination with one or more random effect, taking into account in this way also the heterogeneity among centers because of unobserved centers characteristics.

Keywords: costs and cost analysis, Generalized Linear Models, multicenter studies, myocardial infarction.

Introduction

Preparation of an economic evaluation in conjunction with the analysis of a clinical trial has become a common practice, because of the challenging opportunity of catching patient-specific data on costs and outcomes. In order to assemble large sample sizes in a short period and to improve results, multicenter studies are carried out, often at international level. When health outcomes and resource utilization are collected in several sites, numerous methodological problems arise. A correlation in costs and outcomes between patients recruited in particular centers may be expected, given that centers often differ in clinical practice and patient case-mix. Indeed, patients in the same center undergo a set of center-specific treatment practices and evaluation of endpoints, with perhaps a unique pattern of communications among the patients within the given center. As a consequence, besides heterogeneity in the clinical factors (between-patient variability), analysis should appropriately address the heterogeneity among centers (between-hospital variability) [1]. This implies that outcomes of patients within a hospital are generally more correlated with each other than with patients from other hospitals: this is the so-called cluster effect in the correlated data modeling literature, where indeed the hospital is the cluster. Patients within a given hospital may share characteristics (a specific disease, a sociodemographic subgroup, the impact of hospital, physicians, and process-related characteristics), and their outcomes are unlikely to be truly independent of one another [2]. Still, heterogeneity across centers may be particularly apparent when centers come from different countries [3]. A strict protocol, with a close specification of a set of sensitive inclusion/exclusion criteria, can reduce heterogeneity of patients and limit the impact of confounding factors, allowing outcome results to be pooled. The same cannot always be said for costs. Indeed, main differences in costs can be attributable also to the center-specific characteristics, where organizational and managerial aspects play a major role. Differences in practice patterns, use of resources, and costs between centers can shape the economic impact of the treatment [4].

To avoid misleading conclusions in multi-center economic evaluations the center effect needs to be appropriately considered. False inference can be drawn ignoring the structure of the data and the crude difference in costs between centers may indeed provide an unrealistic indication of the true differences between them [5]. Several approaches have thus been attempted to deal with such phenomenon, ranging from the very first studies relying upon ordinary least squares (OLS) models [6–9], up to more recent contributions based on multi-level modeling approaches [1,5,10] and more complex distributional assumptions [10], where the assumption of independence among observation is relaxed. In this context of correlated observations, Grieve et al. [10] showed that multilevel Gamma models, are more appropriate than OLS for assessing cost determinants. The lower bias and more precise estimates provided by the Gamma models as compared with OLS and other estimators, like the Cox

Address correspondence to: Michele Petrinco, Public Health and Microbiology, University of Turin, via Santena 7, Turin, 10126, Italy. E-mail: mpetrinco@yahoo.it

10.1111/j.1524-4733.2008.00420.x

© 2008, International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

proportional hazard estimator, were basically due to the capability of the Gamma models to handle skewed data more appropriately [11], releasing the assumptions of symmetry typical of the OLS model based on the Normal distribution.

All these models, nevertheless, treat the center effect in terms of a random effect, which is basically a latent variable mimicking the center effect, for which usually no specific information is collected at the time of study conduction and, consequently, neglected at the analysis stage.

Thus, even though several methods are available for adjusting for the center effect, and their pros and cons have been widely discussed [12], few indications are available in the literature of whether and to what extent the additional information gathered for the characterization of the center is worth the effort.

The aim of this article is to compare several models, which make use of a different amount of information about the enrolling center, to understand and eventually to provide some guidance on how useful it is to consider and collect center-specific variables in the analysis. Such aspects are explored with reference to Cost of Strategies after Myocardial Infarction (COSTAMI), an international randomized trial on costs of uncomplicated AMI.

Materials and Methods

Statistical Models

To model the association of total medical costs to levels of two sets of covariates, one at patient and one at center level, we considered four statistical models, all based on the Gamma distribution (Generalized Linear Models) with a log link, known to have a good fit of positively skewed data, as the cost data often are [11]. Beside the Gamma model a wide set of alternative choices have been proposed, from very simple ones like the log-normal [13] up to more complex models in a fully Bayesian setting [14]. Nevertheless, among the models which are most easily handled by common statistical packages, the Gamma has been shown, in situation without center effects, to be a flexible and perhaps robust alternative in modeling cost distribution.

A Gamma regression model takes the form of:

$$C_i = \beta_0 + \beta x_i + \varepsilon_i \quad \varepsilon_i \sim \text{Gamma}\,(0, \sigma^2) \tag{1}$$

Where, C_i is the continuous outcome, the cost, for the i-th patients; x_i is a vector of values for a set of explanatory variables related to the clinical characteristics of the subject, with associated a vector of slope coefficients β. The coefficient β_0 is the intercept of the model; ε_i is a random error term which represents the unexplained variability between patients and is assumed to be distributed as a Gamma with a mean of 0 and variance σ^2.

In all the versions of the Gamma model we considered, $E(C/x)$ is assumed to exhibits an exponential conditional mean or log-link relationship, i.e., a log-link function [15] for the mean of C given the covariates x:

$$E(C/x) = \exp(x\beta)$$

In the standard version of the model, where all observations are treated as independent, the hierarchical structure of the data is not revealed: all the patients have the same intercept and slope coefficients, no one variable related to the center characteristics was considered, and ε_i is the only component of the total unexplained variability.

When the hierarchical structure of the data is taken into account, e.g., in a multilevel model framework, the way the unexplained variation is modeled changes drastically. In the most basic multi-level model, the so-called random intercept model, the subscript i for the patients and j for the centers, may be written as:

$$C_{ij} = (\beta_0 + u_j) + \beta x_i + \varepsilon_{ij} \quad \varepsilon_{ij} \sim \text{Gamma}\,(0, \sigma^2)$$
$$u_j \sim \text{Normal}\,(0, \tau^2) \tag{2}$$

This model includes an additional term, u_j, which represents the unexplained variation between centers and indicates the random effect of the center on the outcome variable. The random variable u_j applies to the patients in center j and is commonly assumed to be distributed as a Normal with zero mean and constant variance τ^2 that represents the residual variability between centers not explained by the covariates. The residual term ε_{ij} is now a random error term representing the unexplained variation for patients within a center. The intercept for the j-th center (previously given as β_0) is now given as the fixed quantity β_0 plus the random component u_j.

If covariates are available to describe center characteristics, it may be appropriate to include this information in the analysis. One possibility is to include a center-level explanatory variable (or a set of them):

$$C_{ij} = \beta_0 + \beta x_i + \gamma z_j + \varepsilon_{ij} \quad \varepsilon_{ij} \sim \text{Gamma}\,(0, \sigma^2) \tag{3}$$

The center-level covariate z_j, and consequently the associated slope coefficient γ, necessarily take the same value for all patients in a particular center. The center characteristics are thus included in the model as fixed effects.

Another possibility, providing information on center characteristics is available, is to adapt a multi-level Gamma model with random intercept to this last model, which is nothing but the development of the model (2) including additional explanatory variables at the level of the centers:

$$C_{ij} = \beta_0 + \beta x_i + \gamma z_j + u_j + \varepsilon_{ij} \quad \varepsilon_{ij} \sim \text{Gamma}\,(0, \sigma^2)$$
$$u_j \sim \text{Normal}\,(0, \tau^2) \tag{4}$$

The variance term τ^2 represents the residual variability between centers which is not explained by the covariates inserted both at patient and at center level.

The COSTAMI Trial

Between January 1998 and August 2000, 458 patients with a recent uncomplicated myocardial infarction from 10 centers (8 in Italy and 2 in Turkey) were recruited and randomly assigned to early discharge or usual care strategy.

Data were collected within a prospective randomized multicenter trial [16]. The trial [16] compared early discharge strategy, consisting of early (day 3 up to day 5 in case of organizational problems) use of pharmacological stress echocardiography and immediate subsequent discharge in case of a negative result of test (Strategy 1), with usual care strategy, based on clinical evaluation with no stress before discharge (that was on day 7–9) and a symptom limited exercise electrocardiography (ECG) at 2–3 weeks after discharge (Strategy 2), according to present guidelines [17].

Data were collected on patient characteristics, AMI severity measures, prescribed medications, and center characteristics. Total medical costs per patient were measured as the sum of initial hospital costs and follow-up hospital and outpatients costs at year 1. In the analysis we used National Health System reimbursement tariffs from the site of the coordinating center, in the Friuli Venezia Giulia Region, for costing resources calculated in each center. The use of resources was calculated considering direct medical costs of hospitalizations, investigations, and interventions and quantified using the mean reimbursement for the Diagnosis-Related Group and outpatient procedures.

Table 1 Per patient costs according to center characteristics: Me (mean, standard deviation) (25th, 75th percentile)

	N	Cost
Hospitalizations		
≤Me (12,213)	271	2,923 (7,417, 8,602) [2,223, 11,011]
>Me (12,213)	187	4,967 (8,499, 8,100) [2,450, 12,275]
Cardiac department (N)		
= 1	441	3,595 (7,859, 8,408) [2,450, 11,361]
>1	17	4,556 (8,573, 9,006) [2,800, 11,588]
Permanent cardiologist in ER		
Absent	353	3,561 (7,843, 8,630) [2,423, 11,361]
Present	105	4,206 (7,911, 7,654) [2,450, 11,405]
Coronary angioplasty unit		
Absent	233	3,211 (7,659, 8,172) [2,450, 11,238]
Present	225	4,144 (8,066, 8,660) [2,223, 11,588]
Beds		
≤Me (350)	280	3,564 (8,007, 8,656) [2,450, 11,594]
>Me (350)	178	3,884 (7,181, 7,170) [2,450, 10,600]
Patients admitted in ER		
≤Me (245,00)	236	2,800 (6,686, 8,171) [2,223, 5,956]
>Me (24,500)	179	4,494 (8,376, 8,472) [2,450, 11,711]
Cardiac surgery unit		
Absent	349	3,623 (7,968, 8,200) [2,450, 11,613]
Present	109	3,567 (7,509, 9,074) [2,223, 10,244]
Coronary angiography unit		
Absent	274	3,150 (7,344, 7,923) [2,450, 11,011]
Present	184	4,559 (8,627, 9,051) [2,280, 11,946]
Hospitalizations in Cardiology		
≤Me (760)	274	3,595 (7,859, 8,408) [2,450, 11,361]
>Me (760)	184	4,559 (8,627, 9,051) [2,280, 11,946]
Myocardial infarction (N)		
≤Me (300)	274	3,966 (8,024, 8,306) [2,280, 11,711]
>Me (300)	184	3,330 (7,489, 8,652) [2,450, 9,161]
Rest echo exams performed		
≤Me (3,653)	299	3,330 (7,405, 7,895) [2,450, 10,981]
>Me (3,653)	159	4,495 (8,714, 9,263) [2,223, 12,353]
Exercise test exams performed		
≤Me (800)	233	4,844 (8,841, 8,923) [2,322, 12,061]
>Me (800)	225	2,923 (7,027, 7,869) [2,450, 10,183]
Transplants performed		
= 0	391	3,917 (8,001, 8,186) [2,450, 11,575]
>0	67	2,560 (7,029, 9,633) [2,131, 10,308]
Beds in cardiology		
≤Me (21)	246	4,439 (8,253, 7,972) [2,450, 12,061]
>Me (21)	212	3,150 (7,402, 8,885) [2,265, 10,136]
Beds in Coronary intensive unit		
≤Me (6)	314	3,561 (7,678, 8,236) [2,450, 10,974]
>Me (6)	144	3,911 (8,254, 8,028) [2,276, 11,669]
Hearth failures (N)		
≤Me (100)	231	2,923 (7,347, 8,621) [2,450, 9,628]
>Me (100)	227	4,144 (8,025, 8,344) [2,423, 11,394]
Stress echo exams performed		
≤Me (121)	246	5,194 (8,793, 8,202) [2,450, 12,407]
>Me (121)	212	2,923 (7,102, 8,513) [2,223, 10,017]
PTCA performed		
= 0	274	3,150 (7,344, 7,923) [2,450, 11,011]
>0	184	4,559 (8,627, 9,051) [2,280, 11,946]
CABG performed		
= 0	349	3,561 (7,753, 8,458) [2,223, 11,011]
>0	109	3,850 (8,200, 8,454) [2,511, 12,411]

ER, emergency room; Me, median; PTCA, percutaneous transluminal coronary angioplasty; CABG, Coronary artery bypass grafting.

Clinical characteristics of the patients according to the center and their structural characteristics are described in the supplementary materials (Tables 1–3).

Statistical Analysis

The same set of variables was considered, when applicable, for all four models (1–4), including: demographic characteristics, clinical characteristics of the patients, the strategy of treatment, and in the models (3) and (4) an additional set of center level variables for the COSTAMI study pooled together. Influence of center on the marginal estimates for models (1) and (4) were computed using the Preisser and Qaqish influence measure [18], indicating the effect that removing the given center has on the final effect estimates. This takes into account the leverage and residuals in a set of observations to determine their influence on regression parameter estimates and fitted values. Missing values of each variable inserted in the models were removed losing a total of two observations. Variables were included in the analysis on the basis of an informal clinical reasoning with the study investigators on being associated with treatment costs: regarding the clinical characteristics strategy, gender, age, presence of diabetes, and/or hypertension, previous occurrence of AMI and regarding center-related variables coronary angioplasty unit, number of myocardial infarctions, and beds in cardiology. All variables were inserted in the models and the AIC criterion was computed in order to evaluate fit of the models. Although the main hypothesis in the COSTAMI trial was the reduction in costs of the early discharge strategy (1) as compared with the standard one (2), all *P*-values were computed as two-sided, obtaining in this way more conservative estimates of the significance of the effects. Confidence intervals for the intracenter correlation have been obtained using a nonparametric Bootstrap (1000 runs). All analyses have been performed using the R system [19]; the models have been fitted using the mlmRev [20] libraries. In addition, results have been compared with the STATA statistical software [21], estimates, ending up being very similar.

Results

The distribution of total costs according to the center characteristics is shown in Table 1. Missing data incidence in the variables used for modeling purposes was negligible: for patient characteristics on average less than 0.1% of data had a loss of information and for center characteristics all the data were available.

Median patient cost seems directly associated to the number of hospitalizations, possibly because of a larger dimension and a more complex organizational structure. On the other hand, the other hospital characteristics result inversely associated with the observed costs, as a consequence of economies of scale because of the better utilization of available resources and to the major expertise of specialized hospitals.

Median cost varies among centers from 2560€ per patient up to the maximum of 4967€. Strategy 1 shows a lower median cost than usual care strategy, because of anticipated discharge. Fit for models without any center-specific covariate, (1) and (2), is presented in Table 2. Simple center effect adjustment based on a single random effect results in a more marked estimate of the effect of strategy of patient management. In particular, significance of the parameters changes from –0.14 to –0.17 for Strategy 1. Significance of patient management strategy is revised downward adding center information both as fixed and as random terms, i.e., as in models (3) and (4) (details shown in Table 3). Influence of the unobserved center characteristics is shown in Figure 1. Each point represents the effect on the residual that each center has in the model. Thus, the greater the value of the influence measure (*y*-axis), the greater the absolute influence that the center has in the given model. Model M4 has thus an overall maximum influence of 0.53 (Center 8) whereas the M1 model has a maximum influence of 0.17 (Center 7), about three times lower. Notice that incorporating the information on center characteristics highlights the effect of just one center, leaving the influence of the others at the same level as without considering such information. Country effect is almost negligible, as indicated by an analysis of the influence measure, where the average influence for Italian centers is 0.08 and for

Table 2 Gamma and ML Gamma models with log-link estimating the effect of patient variables on total cost: coefficient, standard errors (SE) and two-sided *P*-values

	No center information (Gamma model)			Center as random effect (multilevel Gamma model)		
	Effect	SE	*P*-value	Effect	SE	*P*-value
(Intercept)	9.03	0.16	0.00	9.03	0.17	0.00
Strategy 1 vs. 2	–0.14	0.10	0.09	–0.17	0.10	0.05
Gender (male vs. female)	–0.10	0.14	0.24	–0.10	0.14	0.24
Age >65 vs. ≤65	–0.07	0.12	0.26	–0.04	0.12	0.35
Hypertension (presence vs. absence)	0.20	0.10	0.03	0.22	0.10	0.02
Previous AMI (presence vs. absence)	–0.14	0.21	0.25	–0.10	0.21	0.32
Diabetes (presence vs. absence)	0.15	0.14	0.15	0.13	0.14	0.17
τ^2				0.02	0.13	
Within center correlation (95% confidence interval)				0.11 (0.04–0.21)		

Turkish centers 0.10, for model M1. For Model M4 the average influence for Italian centers is 0.12 and for Turkish centers 0.08, with the increase in the difference because of the effect of the General Hospital of San Giovanni Rotondo (Foggia, Italy). Most of the residual influence is eventually given by the heterogeneity among Italian centers.

Discussion

Finding good predictors of subsequent cost is notoriously difficult, in both health economic evaluations [22] and in insurance risk assessment. Prior resource use is sometimes the only really important predictor of subsequent resource use [5]. In most of

Table 3 Models with center characteristics, included as fixed effects and random effects, always using a random intercept: coefficient, standard errors (SE) and two-sided *P*-values

	Center characteristics as fixed effects			Center characteristics as random effects		
	Effect	SE	*P*-value	Effect	SE	*P*-value
(Intercept)	9.07	0.20	0.00	9.06	0.27	0.00
Strategy 1 vs. 2	–0.14	0.10	0.09	–0.18	0.10	0.04
Gender (male vs. female)	–0.08	0.14	0.28	–0.10	0.14	0.24
Age >65 vs. ≤65	–0.06	0.12	0.32	–0.03	0.12	0.39
Hypertension (presence vs. absence)	0.20	0.10	0.03	0.22	0.10	0.02
Previous AMI (presence vs. absence)	–0.11	0.22	0.30	–0.08	0.22	0.36
Diabetes (presence vs. absence)	0.15	0.14	0.15	0.12	0.14	0.20
Beds in Cardiology Department	0.00	0.00	0.28			
Primary PTCA Setting	0.01	0.13	0.47			
Number of MI treated	–0.01	0.01	0.18			
Random effects						
Beds in Cardiology Department				0.01	0.01	0.39
Primary PTCA Setting				–0.04	0.22	0.43
Number of MI treated				–0.01	0.01	0.40
τ^2 (between center variability)	0.03	0.16		0.04	0.09	
Within Center correlation (95% confidence interval)	0.13 (0.05–0.25)			0.09 (0.04–0.22)		

AMI, acute myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; MI, myocardial infarction.

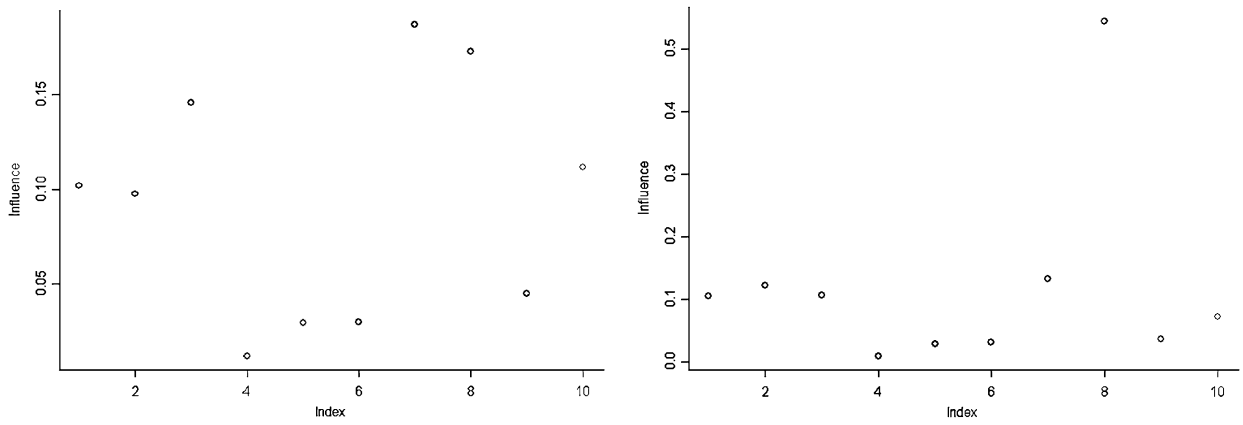

Figure 1 Influence plots. Left panel refers to the marginal model M1, right panel to the marginal model M4. Influence is the Preisser and Qaqish measure [19].

the multi-center studies, balance in patient characteristics is granted by the randomization procedure adopted for the study. In this study, we indeed observed a high level of homogeneity in patients' baseline characteristics in each center. Nevertheless, in such multicenter studies, patients were assigned at specified strategies of treatment in each hospital but were treated by different medical staff. With respect to the between-hospital variability, the heterogeneity of the hospitals clinical practice seems to be more significant than the patient case-mix one. Overall within-center correlation was perhaps small, but still influencing the estimates, as shown by the changes in effect when different hierarchical structures are used and different degree of information on the center characteristic is put in the model.

Center Effect without Center-Specific Information

In common situations, no covariates are available to describe the center selection process, as no control is over the factors contributing to a center investigator choice to participate in the study. In this case, the common approach is to model the center effect using a random intercept in the model [23]. This correction usually inflates standard errors of the estimates of the parameters which are related to variables describing center characteristics. This effect can be additionally emphasized by the estimation procedure adopted, when based on shrinkage. Indeed, the effect of Strategy 1 is highly dependent on adjustment by center effect, varying at about 26% (from –0.14 to –0.17). More interestingly, significance of the parameter changes from 0.09 to 0.05, with consequent important changes in the results interpretation. The fact that the effect of the strategy is dependent on the proper modeling of the center is entirely because of the fact that the data are collected in different sites.

Center Effect with Center-Specific Information

When information on some characteristics of the centers is available, further information can be added in the model. First, characteristics of the centers should involve information on activity levels and on size of the structure. If available, additional information on the population referring to the center could also be helpful, but it is not always the case; second, treating such information can be accomplished in two ways, by using the information at center level as fixed effects, or as random effects. In Table 3 the two approaches are compared. First, it has to be noticed that the cost reductions attributable to Strategy 1 in the final model are significant at 0.05 level. This is a sign that the efficacy of the strategy is dependent on the center where it is applied. This is particularly true in a trial setting like the COSTAMI, where the intervention is essentially focused on the criteria over patient management and discharge, all being clearly related to health-care organization.

In the fixed effect model, the idea is that the effect of the number of myocardial infarction (MI) treated (a possible proxy for center experience) directly influences the cost of patient care, having already discounted for a set of relevant covariates possibly related to expenditure.

Study Limitations

Some limitations of the study must be acknowledged. First, data were collected within one randomized international multicenter trial over two countries, and therefore costs in medical care may differ substantially between participating institutions in different countries, where differences can be attributable to the different health-care systems and incentives, and differences in reimbursement mechanisms at the national or local level. Second, although the set of variables collected for describing the center characteristics covers a sensitive range of issues for what concerns the patients' management, still they are not exhausting all possible information. This may result in a bias of the analysis, which can be reduced only partially by the inclusion of a latent variable trying to capture unmeasured center characteristics. Our analysis relies on estimates of resource use from patients in all countries (fully pooled) and use a one-country costing approach, applying unit cost estimates from one country to resource use in all countries [4]. In this way, patient-level relationship between use of resources and costs are not maintained. The impact of this method may depend on the differences in costs and use of resources between centers in the different countries. Nevertheless, because of the observed distribution of centers in the different countries (eight from Italy and two from Turkey), to explicitly consider the country effect in the same model with the center was not advisable, given the (in one case complete) aliasing between center and country.

Second, in the estimation of the use of resources we apply a low-cost approach which considers only the major relevant sources of cost during 1-year follow-up and not the full cost of care.

Finally, the impact of center variables on outcome estimates has been evaluated with reference to a real trial, limiting results generalizability to other situations. Nevertheless, this is the first contribution which has not used results based on simulation or theoretical arguments.

Final Remarks

This study, with reference to a real multi-center trial on costs of treatment of AMI, and using best fitting Gamma models, shows that center information cannot be neglected and should be collected and inserted in the analysis, better in combination with latent variables, in order to capture also the heterogeneity between centers because of unobserved centers characteristics.

Supplementary Materials

Supplementary material for this article can be found at: http://www.ispor.org/publications/value/ViHsupplementary.asp

The study was partially supported by the Compagnia di San Paolo and by the Ricerca Sanitaria Finalizzata 2006, Regione Piemonte.

Source of financial support: This study was supported by the Compagnia di San Paolo.

References

1 Manca A, Rice N, Sculpher MJ, Briggs AH. Assessing generalisability by location in trial-based cost-effectiveness analysis: the use of multilevel models. Health Econ 2005;14:471–85.
2 Austin PC, Tu JV, Alter DA. Comparing hierarchical modeling with traditional logistic regression analysis among patients hospitalized with acute myocardial infarction: should we be analyzing cardiovascular outcomes data differently? Am Heart J 2003; 145:27–35.
3 Cook JR, Drummond M, Glick H, Heyse JF. Assessing the appropriateness of combining economic data from multinational clinical trials. Stat Med 2003;22:1955–76.
4 Reed SD, Anstrom KJ, Bakhai A, et al. Conducting economic evaluations alongside multinational clinical trials: toward a research consensus. Am Heart J 2005;149:434–43.
5 Nixon RM, Thompson SG. Methods for incorporating covariate adjustment, subgroup analysis and between-centre differences into cost-effectiveness evaluations. Health Econ 2005;14:1217–29.

6 Coyle D, Drummond MF. Analyzing differences in the costs of treatment across centres within economic evaluations. Int J Technol Assess Health Care 2001;17:155–63.
7 Grieve R, Dundas R, Beech R, Wolfe C. The development and use of a method to compare the costs of acute stroke across Europe. Age Ageing 2001;30:67–72.
8 Koopmanschap MA, Touw KC, Rutten FF. Analysis of costs and cost-effectiveness in multinational trials. Health Policy 2001;58: 175–86.
9 Willke RJ, Glick HA, Polsky D, Schulman K. Estimating country-specific cost-effectiveness from multinational clinical trials. Health Econ 1998;7:481–93.
10 Grieve R, Nixon R, Thompson SG, Normand C. Using multilevel models for assessing the variability of multinational resource use and cost data. Health Econ 2005;14:185–96.
11 Basu A, Manning WG, Mullahy J. Comparing alternative models: log vs. Cox proportional hazard? Health Econ 2004;13:749–65.
12 Localio AR, Berlin JA, Ten Have TR, Kimmel SE. Adjustments for centre in multicentre studies: an overview. Ann Intern Med 2001;135:112–23.
13 Manning WG. The logged dependent variable, heteroscedasticity, and the retransformation problem. J Health Econ 1998;17:283–95.
14 Cooper NJ, Sutton AJ, Mugford M, Abrams KR. Use of bayesian markov chain monte carlo methods to model cost-of-illness data. Med Decis Making 2003;23:38–53.
15 McCullagh P, Nelder JA. Generalized Linear Models (2nd ed.). London: Chapman & Hall, 1989.
16 Desideri A, Fioretti PM, Cortigiani L, et al. Cost of strategies after myocardial infarction (COSTAMI): a multicentre, international, randomized trial for cost-effective discharge after uncomplicated myocardial infarction. Eur Heart J 2003;24: 1630–9.
17 Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA Guidelines for the management of patients with acute myocardial infarction: executive summary and recommendations: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). Circulation 1999;100:1016–30.
18 Preisser J, Qaqish B. Deletion diagnostics for generalized estimating equations. Biometrika 1996;83:551–62.
19 R Development Core Team. R: A language and Environment for Statistical Computing. Vienna: R Foundation for Statistical Computing. ISBN 3-900051-07-0, URL http://www.R-project.org [Accessed April 24, 2007).
20 Bates D. Package: mlmRev. Examples from Multilevel Modelling Software Review, 2006. Available from: http//cran.r-project.org/ [Accessed January 18, 2006].
21 STATA Corporation. STATA Release 8.2 for Windows. College Station, TX: 2004.
22 Briggs AH, Gray AM. Handling uncertainty in economic evaluations of healthcare interventions. BMJ 1999;319:635–8.
23 Goldstein H. Multilevel Statistical Models (3rd ed.). London, Arnold: Kendall's library of Statistics, 2003.